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Attorney Docket No. P32162C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Hatton, et al.
Predecessor Serial No.	:	09/807,275
Filed	:	19 December 2001

For: **NAPHTHRYDINE COMPOUNDS AND THEIR AZAISOSTERIC ANALOGUES AS ANTIBACTERIALS**

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

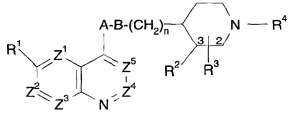
Sir:

The subject application is a continuation of USSN 09/807,275, filed April 11, 2001. Prior to the first Office Action on the merits, the Applicants request entry of the following amendment.

IN THE SPECIFICATION:

Please delete claims 1-12 and insert the following claims:

13. A compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N and the remainder are CH;

R^1 is hydrogen, hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, NH_2CO, hydroxy, thiol, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted (C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; nitro; trifluoromethyl; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups;

either R^2 is hydrogen; and
R^3 is in the 2- or 3-position and is hydrogen or (C_{1-6})alkyl or (C_{2-6})alkenyl optionally substituted with 1 to 3 groups selected from:

thiol; halogen; (C_{1-6})alkylthio; trifluoromethyl; azido; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; aminocarbonyl wherein the amino group is optionally mono- or disubstituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl]; oxo; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

R^3 is in the 3-position and R^2 and R^3 together are a divalent residue $=CR^{5'}R^{6'}$ where $R^{5'}$ and $R^{6'}$ are independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, aryl(C_{1-6})alkyl and aryl(C_{2-6})alkenyl, any alkyl or alkenyl moiety being optionally substituted by 1 to 3 groups selected from those listed above for substituents on R^3;

R^4 is a group $-CH_2-R^5$ in which R^5 is selected from:

(C_{3-12})alkyl; hydroxy(C_{3-12})alkyl; (C_{1-12})alkoxy(C_{3-12})alkyl; (C_{1-12})alkanoyloxy(C_{3-12})alkyl; (C_{3-6})cycloalkyl(C_{3-12})alkyl; hydroxy-, $(C_{1-}$

12)alkoxy- or (C_{1-12})alkanoyloxy-(C_{3-6})cycloalkyl(C_{3-12})alkyl; cyano(C_{3-12})alkyl; (C_{2-12})alkenyl; (C_{2-12})alkynyl; tetrahydrofuryl; mono- or di-(C_{1-12})alkylamino(C_{3-12})alkyl; acylamino(C_{3-12})alkyl; (C_{1-12})alkyl- or acyl-aminocarbonyl(C_{3-12})alkyl; mono- or di- (C_{1-12})alkylamino(hydroxy) (C_{3-12})alkyl; optionally substituted phenyl(C_{1-2})alkyl, phenoxy(C_{1-2})alkyl or phenyl(hydroxy)(C_{1-2})alkyl; optionally substituted diphenyl(C_{1-2})alkyl; optionally substituted phenyl(C_{2-3})alkenyl; optionally substituted benzoyl or benzoylmethyl; optionally substituted heteroaryl(C_{1-2})alkyl;and optionally substituted heteroaroyl or heteroaroylmethyl;

n is 0, 1 or 2;

A is NR^{11}, O, $S(O)_x$ or CR^6R^7 and B is NR^{11}, O, $S(O)_x$ or CR^8R^9 where x is 0, 1 or 2 and wherein:
each of R^6 and R^7 R^8 and R^9 is independently selected from: H; thiol; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{1-6})alkenyl;
or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;
or R^6 and R^8 together represent –O- and R^7 and R^9 are both hydrogen;
or R^6 and R^7 or R^8 and R^9 together represent oxo;
and each R^{11} is independently H, trifluoromethyl, (C_{1-6})alkyl, (C_{1-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, aminocarbonyl wherein the amino group is optionally mono- or di-substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{1-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{1-6})alkenyl;

provided that A and B cannot both be selected from NR^{11}, O and $S(O)_x$ and when one of A and B is CO the other is not CO, O or $S(O)_x$.

14. A compound according to claim 13 wherein Z^1 is N and Z^2-Z^5 are each CH or Z^5 is N and Z^1-Z^4 are each CH.

15. A compound according to claim 13 wherein R^1 is methoxy, amino(C_{3-5})alkyloxy, guanidino(C_{3-5})alkyloxy or fluoro, most preferably methoxy.

16. A compound according to claim 13 wherein R^3 is in the 3-position and is aminocarbonyl(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl or 1,2-dihydroxy(C_{2-6})alkyl optionally substituted on the hydroxy group(s).

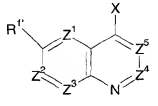
17. A compound according to claim 13 wherein AB is NHCO, $NHCOCH_2$ or $CH_2CH(OH)CH_2$.

18. A compound according to claim 13 wherein R^4 is (C_{5-10})alkyl, unsubstituted phenyl(C_{2-3})alkyl or unsubstituted phenyl(C_{3-4})alkenyl.

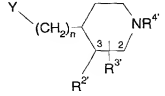
19. A compound according to claim 13 selected from:
[3R, 4S]-1-Heptyl-4-[N-methyl-N-(6-methoxy-quinazolin-4-yl)-2-aminoethyl]-3-ethenylpiperidine;
[3R, 4S]-1-Heptyl-4-[2-(6-methoxyquinazolin-4-oxy)ethyl]-3-ethenylpiperidine;
1-Heptyl-4-(6-methoxy-1,5-naphthyridin-4-yl)aminocarbonyl piperidine;
[3R, 4S]-1-Heptyl-3-ethenyl-4-N-(6-methoxy-1,5-naphthyridin-4-yl)-piperidineacetamide;
[3R,4S]-1-Heptyl-3-ethenyl-4-[2-(R,S)-hydroxy-3-(6-methoxy-1,5-naphthyridin-4-yl)propyl]piperidine;
[3R,4S]-1-Heptyl-4-N-(6-methoxy-1,5-naphthyridin-4-yl)-3,4-piperidinediacetamide;
[3R,4S]-1-Heptyl-4-N-(6-methoxy-1,5-naphthyridin-4-yl)-3-(1-(R,S),2-dihydroxyethyl)-piperidineacetamide;
[3R, 4S]-1-Heptyl-3-ethenyl-4-N-(6-methoxy-cinnolin-4-yl)-piperidineacetamide, [or a pharmaceutically acceptable derivative of any of the foregoing compounds.

20. A process for preparing compounds of formula (I), or a pharmaceutically acceptable derivative thereof according to claim 13, which process comprises:

(a) reacting a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

wherein Z^1, Z^2, Z^3, Z^4 and Z^5, m, n, R^1, R^2, R^3 and R^4 are as defined in formula (I), and X and Y may be the following combinations:

(i) X is M and Y is $CH_2CO_2R^X$

(ii) X is CO_2R^Y and Y is $CH_2CO_2R^X$

(iii) one of X and Y is $CH=SPh_2$ and the other is CHO

(iv) X is CH_3 and Y is CHO

(v) X is CH_3 and Y is CO_2R^X

(vi) X is $CH_2CO_2R^Y$ and Y is CO_2R^X

(vii) X is $CH=PR^Z_3$ and Y is CHO

(viii) X is CHO and Y is $CH=PR^Z_3$

(ix) X is halogen and Y is $CH=CH_2$

(x) one of X and Y is COW and the other is $NHR^{11'}$ or NCO

(xi) one of X and Y is $(CH_2)_p$-V and the other is $(CH_2)_qNHR^{11'}$, $(CH_2)_qOH$, $(CH_2)_qSH$ or $(CH_2)_qSCOR^X$ where p+q=1

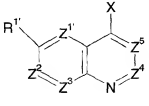
(xii) one of X and Y is CHO and the other is $NHR^{11'}$

(xiii) one of X and Y is OH and the other is $-CH=N_2$

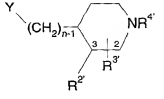
in which V and W are leaving groups, R^X and R^Y are (C_{1-6})alkyl and R^Z is aryl or (C_{1-6})alkyl;

or

(b) reacting a compound of formula (IV) with a compound of formula (Vb):



(IV)



(Vb)

wherein Z^1, Z^2, Z^3, Z^4 and Z^5, m, n, R^1, R^2, R^3 and R^4 are as defined in formula (I), X is $CH_2NHR^{11'}$ and Y is CHO or COW or X is CH_2OH and Y is $-CH=N_2$;

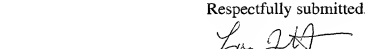
in which $R^{11'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are R^{11}, R^1, R^2, R^3 and R^4 or groups convertible thereto, and thereafter optionally or as necessary converting $R^{11'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ to $R^{11'}$, R^1, R^2, R^3 and R^4, converting A-B to other A-B, interconverting R^{11}, R^1, R^2, R^3 and/or R^4 and forming a pharmaceutically acceptable derivative thereof.

21. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 13, and a pharmaceutically acceptable carrier.

22. A method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment of an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 13.

If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned attorney.

Respectfully submitted,



Loretta J. Henderson
Attorney for Applicants
Registration No. 37,347

SMITHKLINE BEECHAM CORPORATION
Corporate Intellectual Property UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-6897
Facsimile (610) 270-5090
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